454,096 No 7/8

STIC-ILL

From: Bahar, Mojdeh
Sent: Monday, July 07, 2003 6:03 PM
To: STIC-ILL
Subject: article

Could you please pull the following artcle for me.	
1: Anaesthesia. 1970 Apr;25(2):184-90	

Extradural blockade with bupivacaine. A double blind trial of bupivacaine with adrenaline 1-200,000, and bupivacaine plain.

Waters HR, Rosen N, Perkins DH.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 4909431 [PubMed - indexed for MEDLINE]

Thank you,
Mojdeh Bahar

514/605 514/727 epinephrine + levonordefrin

```
=> s ibutilide
L1            4 IBUTILIDE

=> s ibutilide/cn
L2            1 IBUTILIDE/CN

=> d

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   122647-31-8  REGISTRY
CN   Methanesulfonamide, N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]-
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Methanesulfonamide, N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]-,
     (.+-.)-
OTHER NAMES:
CN   Ibutilide
DR   100632-81-3
MF   C20 H36 N2 O3 S
CI   COM
SR   US Adopted Names Council
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, DDFU, DIOGENES, DRUGNL,
       DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, SYNTHLINE,
       TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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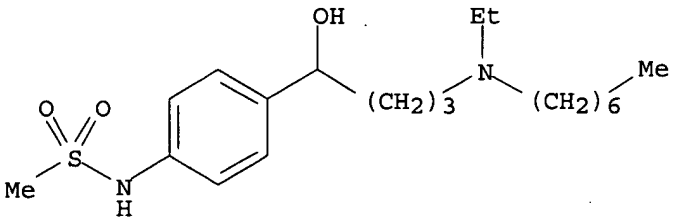



```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

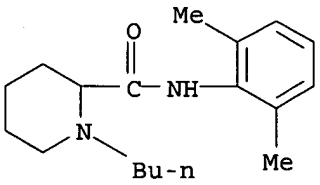
              86 REFERENCES IN FILE CA (1957 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              86 REFERENCES IN FILE CAPLUS (1957 TO DATE)


=> s bupivacaine/cn
L3            1 BUPIVACAINE/CN

=> d

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   38396-39-3  REGISTRY
CN   2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)- (9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   2-Piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, (.+-.)-
OTHER NAMES:
CN   (.+-.)-Bupivacaine
CN   1-Butyl-2',6'-pipecoloxylidide
CN   Anekain
CN   Bupivacaine
CN   Bupivan
CN   Carbostesin
```

CN DL-Bupivacaine
CN Marcaine
CN Win 11318
DR 2180-92-9
MF C18 H28 N2 O
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2293 REFERENCES IN FILE CA (1957 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2294 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> fil caplus medline embase biosis uspatfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	16.82	17.03

FILE 'CAPLUS' ENTERED AT 18:06:08 ON 07 JUL 2003
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FILE 'USPATFULL' ENTERED AT 18:06:08 ON 07 JUL 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> s ibutilide or 122647-31-8/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L4 1047 IBUTILIDE OR 122647-31-8/RN

=> s bupivacaine or 38396-39-3/rn

'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L5 33789 BUPIVACAINE OR 38396-39-3/RN

=> s l4 and l5
L6 18 L4 AND L5

=> s l6 and py<2001
3 FILES SEARCHED...
L7 3 L6 AND PY<2001

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 3 DUP REM L7 (0 DUPLICATES REMOVED)

=> d l8 1-3 ab bib kwic

L8 ANSWER 1 OF 3 USPATFULL
AB Methods, devices, and compositions for treatment of dysmenorrhea comprise an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea. The drug delivery system can be a tampon device, vaginal ring, pessary, tablet, suppository, vaginal medicated tampon, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, paste, solution or gel. The system delivers a higher concentration to the muscle of the uterus, the primary site for the dyskinetic muscle contraction, which is the pathophysiologic cause of dysmenorrhea.
AN 2000:87740 USPATFULL
TI Device and method for treatment of dysmenorrhea
IN Harrison, Donald C., Cincinnati, OH, United States
Liu, James H., Cincinnati, OH, United States
Ritschel, Wolfgang A., Cincinnati, OH, United States
Stern, Roger A., Cupertino, CA, United States
PA UMD, Inc., Cincinnati, OH, United States (U.S. corporation)
PI US 6086909 20000711 <--
AI US 1999-249963 19990212 (9)
RLI Continuation-in-part of Ser. No. US 1998-79897, filed on 15 May 1998
PRAI US 1997-49325P 19970611 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Azpuru, Carlos A.
LREP Verny, Hana
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 24 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6086909 20000711 <--
SUMM . . . include Aspirin, Ibuprofen, Indomethacin, Phenylbutazone, Bromfenac, Fenamate, Sulindac, Nabumetone, Ketorolac, and Naproxen. Examples of local anesthetics include Lidocaine, Mepivacaine, Etidocaine, **Bupivacaine**, 2-Chloroprocaine hydrochloride, Procaine, and Tetracaine hydrochloride. Examples of calcium channel antagonists include Diltiazem, Israpidine, Nimodipine, Felodipine, Verapamil, Nifedipine, Nicardipine, and Bepridil. Examples of potassium channel blockers include Dofetilide, E-4031, Almokalant, Sematilide, Ambasilide, Azimilide, Tedisamil, RP58866, Sotalol, Piroxicam, and **Ibutilide**. Examples of .beta.-adrenergic agonists include Terbutaline, Salbutamol, Metaproterenol, and Ritodrine. Vasodilators, which are believed to relieve muscle spasm in the. . .

SUMM . . . include Aspirin, Ibuprofen, Indomethacin, Phenylbutazone, Bromfenac, Fenamate, Sulindac, Nabumetone, Ketorolac, and Naproxen. Examples of local anesthetics include Lidocaine, Mepivacaine, Etidocaine, **Bupivacaine**, 2-Chloroprocaine hydrochloride, Procaine, and Tetracaine hydrochloride. Examples of COX-2 inhibitors include Celecoxib, Meloxicam and Flosulide. Examples of calcium channel antagonists. . . Nicardipine, Piroxicam, and Bepridil. Examples of potassium channel blockers include Dofetilide, E-4031, Almokalant, Sematilide Ambasilide, Azimilide, Tedisamil, RP58866, Sotalol, and **Ibutilide**. Examples of .beta.-adrenergic agonists include Terbutaline, Salbutamol, Metaproterenol, and Ritodrine. Vasodilators include nitroglycerin, isosorbide dinitrate and isosorbide mononitrate.

DETD Preferred NSAIDs include Aspirin, Ibuprofen, Indomethacin, Phenylbutazone, Bromfenac, Sulindac, Nabumetone, Ketorolac, and Naproxen. Preferred local anesthetics include Lidocaine, Mepivacaine, Etidocaine, **Bupivacaine**, 2-Chloroprocaine hydrochloride, Procaine, and Tetracaine hydrochloride. Preferred calcium channel antagonists include Diltaizem, Israpidine, Nimodipine, Felodipine, Verapamil, Nifedipine, Nicardipine, and Bepridil. Preferred potassium channel blockers include Dofetilide, E-4031, Imokalant, Sematilide, Ambasilide, Azimilide, Ted isamil, RP58866, Sotalol, Piroxicam, and **Ibutilide**. Preferred .beta.-adrenergic agonists include Terbutaline, Salbutamol, Metaproterenol, and Ritodrine. Vasodilators, which are believed to relieve muscle spasm in the uterine. . .

DETD . . . Phenylbutazone (50 mg, P-8386, Sigma), Bromfenac (50 mg), Naproxen (550 mg), Lidocaine (100 mg), Mepivacaine (0.2 mg), Etidocaine (200 mg), **Bupivacaine** (100 mg), 2-Chloroprocaine hydrochloride (100 mg), Procaine (200 mg, P-9879, Sigma), Tetracaine hydrochloride (20 mg, T-7508, Sigma), Diltaizem (60 mg),. . . (1 mg), Sematilide (1 mg), Ambasilide (1 mg), Azimilide (1 mg), Tedisamil (100 mg), RP58866 (100 mg), Sotalol (240 mg), **Ibutilide** (1 mg), Terbutaline (5 mg), Salbutamol (1 mg), Piroxicam (20 mg), Metaproterenol sulphate (20 mg), nitroglycerin (3 mg), isosorbide dinitrate. . .

DETD . . . Phenylbutazone (50 mg, P-8386, Sigma), Bromfenac (50 mg), Naproxen (550 mg), Lidocaine (100 mg), Mepivacaine (0.2 mg), Etidocaine (200 mg), **Bupivacaine** (100 mg), 2-Chloroprocaine hydrochloride (100 mg), Procaine (200 mg, P-9879, Sigma), Tetracaine hydrochloride (20 mg, T-7508, Sigma), Diltaizem (60 mg),. . . (1 mg), Sematilide (1 mg), Ambasilide (1 mg), Azimilide (1 mg), Tedisamil (100 mg), RP58866 (100 mg), Sotalol (240 mg), **Ibutilide** (1 mg) Terbutaline (5 mg), Salbutamol (1 mg), Metaproterenol sulphate (20 mg), nitroglycerin (3 mg), isosorbide dinitrate (40 mg), isosorbide. . .

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AB Methods, devices, and compns. for treatment of dysmenorrhea comprise an intravaginal drug delivery system contg. an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea. The drug delivery system can be a tampon device, vaginal ring, pessary, tablet, suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream lotion, foam, ointment, paste soln., or gel. The system delivers a higher concn. to the muscle of the uterus, the primary site for the dyskinetic muscle contraction, which is the pathophysiol. cause of dysmenorrhea. Verapamil vaginal suppositories were prepd. contg. Suppocire AS2, HPMC, and Transcutol.

AN 1999:7775 CAPLUS

DN 130:57225

TI Device and method for treatment of dysmenorrhea

IN Harrison, Donald C.; Liu, James H.; Ritschel, Wolfgang A.; Stern, Roger A.

PA UMD, Inc., USA

SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2

DT Patent

LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9856323	A1	19981217	WO 1998-US10785	19980610	<--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	US 6197327	B1	20010306	US 1998-79897	19980515	
	AU 9876976	A1	19981230	AU 1998-76976	19980610	<--
	AU 735407	B2	20010705			
	EP 988009	A1	20000329	EP 1998-924918	19980610	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	BR 9810089	A	20000808	BR 1998-10089	19980610	<--
	NZ 502120	A	20020426	NZ 1998-502120	19980610	
	JP 2002515069	T2	20020521	JP 1999-502556	19980610	
	NZ 508130	A	20020301	NZ 2000-508130	20001113	
PRAI	US 1997-49325P	P	19970611			
	US 1998-79897	A	19980515			
	NZ 1998-502120	A1	19980610			
	WO 1998-US10785	W	19980610			

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

PI WO 9856323 A1 **19981217**

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9856323	A1	19981217	WO 1998-US10785	19980610	<--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	US 6197327	B1	20010306	US 1998-79897	19980515	
	AU 9876976	A1	19981230	AU 1998-76976	19980610	<--
	AU 735407	B2	20010705			
	EP 988009	A1	20000329	EP 1998-924918	19980610	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	BR 9810089	A	20000808	BR 1998-10089	19980610	<--
	NZ 502120	A	20020426	NZ 1998-502120	19980610	
	JP 2002515069	T2	20020521	JP 1999-502556	19980610	
	NZ 508130	A	20020301	NZ 2000-508130	20001113	

IT 50-33-9, Phenylbutazone, biological studies 50-78-2, Aspirin 52-53-9, Verapamil 53-86-1, Indomethacin 55-63-0, Nitroglycerin 59-46-1, Procaine 87-33-2, Isosorbide dinitrate 91-40-7, Fenamic acid 96-88-8, Mepivacaine 136-47-0, Tetracaine hydrochloride 137-58-6, Lidocaine 586-06-1, Metaproterenol 3858-89-7, 2-Chloroprocaine hydrochloride 3930-20-9, Sotalol 15687-27-1, Ibuprofen 16051-77-7, Isosorbide mononitrate 18559-94-9, Salbutamol 21829-25-4, Nifedipine 22204-53-1, Naproxen 23031-25-6, Terbutaline 26652-09-5, Ritodrine 36322-90-4, Piroxicam 36637-18-0, Etidocaine 38194-50-2, Sulindac **38396-39-3, Bupivacaine** 42399-41-7, Diltiazem 42924-53-8, Nabumetone 55985-32-5, Nicardipine 64706-54-3, Bepridil 66085-59-4, Nimodipine 72509-76-3, Felodipine 74103-06-3, Ketorolac 75695-93-1, Isradipine 83991-25-7, Ambasilide 90961-53-8, Tedisamil

91714-94-2, Bromfenac 101526-83-4, Sematilide 113559-13-0, E-4031
115256-11-6, Dofetilide 121277-95-0, RP58866 **122647-31-8**,
Ibutilide 123955-10-2, Almokalant 149908-53-2, Azimilide
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vaginal drug delivery devices for treatment of dysmenorrhea)

L8 ANSWER 3 OF 3 USPATFULL
AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.
AN 1998:98932 USPATFULL
TI DHA-pharmaceutical agent conjugates of taxanes
IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)
PI US 5795909 19980818 <--
AI US 1996-651312 19960522 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Wolf, Greenfield & Sacks, P.C.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5795909 19980818 <--
DETD Anesthetic: Aliflurane; Benoxinate Hydrochloride; Benzocaine; Biphenamine Hydrochloride; **Bupivacaine** Hydrochloride; Butamben; Butamben Picrate; Chloroprocaine Hydrochloride; Cocaine; Cocaine Hydrochloride; Cyclopropane; Desflurane; Dexivacaine; Diamocaine Cyclamate; Dibucaine; Dibucaine Hydrochloride; Dyclonine Hydrochloride; Enflurane; . . .
DETD . . . Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobuline; Edifolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; **Ibutilide** Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium. . .

=> s ibutilide or 122647-31-8/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L9 1047 IBUTILIDE OR 122647-31-8/RN

=> s pain or analgesia or analgesic
L10 803098 PAIN OR ANALGESIA OR ANALGESIC

=> s l9 and l10
L11 64 L9 AND L10

=> s local anesthetic or lidocaine or bupivacaine or dibucaine or articaine or levobupivacaine or ropivacaine or todocaine or prilocaine or mepivacaine or etidocaine
L12 144757 LOCAL ANESTHETIC OR LIDOCAINE OR BUPIVACAINE OR DIBUCAINE OR ARTICAINE OR LEVOBUPIVACAINE OR ROPIVACAINE OR TODOCAINE OR PRILOCAINE OR MEPIVACAINE OR ETIDOCAINE

```
=> s l9 and l12
L13         164 L9 AND L12

=> s l11 and l12
L14          47 L11 AND L12

=> s epinephrine or adrenaline or levonordefin or vasoconstrict?
L15      328921 EPINEPHRINE OR ADRENALINE OR LEVONORDEFIN OR VASOCONSTRICT?

=> s l14 and l15
L16          18 L14 AND L15

=> s l16 and py<2002
   3 FILES SEARCHED...
   4 FILES SEARCHED...
L17           5 L16 AND PY<2002

=> d l17 1-5 ab bib kwic

L17  ANSWER 1 OF 5  USPATFULL
AB      A method is provided for increasing the permeability of skin or mucosal
        tissue to topically or transdermally administered pharmacologically or
        cosmeceutically active agents. The method involves use of a specified
        amount of a hydroxide-releasing agent, the amount optimized to increase
        the flux of the active agent through a body surface while minimizing the
        likelihood of skin damage, irritation or sensitization. Topically
        applied formulations and drug delivery devices employing
        hydroxide-releasing agents as permeation enhancers are provided as well.
AN      2001:229217  USPATFULL
TI      Hydroxide-releasing agents as skin permeation enhancers
IN      Luo, Eric C., Plano, TX, United States
        Jacobson, Eric C., San Diego, CA, United States
        Hsu, Tsung-Min, San Diego, CA, United States
PI      US 2001051166      A1   20011213                                  <--
        US 6586000         B2   20030701
AI      US 2000-738410     A1   20001214 (9)
RLI     Continuation-in-part of Ser. No. US 2000-569889, filed on 11 May 2000,
        PENDING Continuation-in-part of Ser. No. US 1999-465098, filed on 16 Dec
        1999, PENDING
DT      Utility
FS      APPLICATION
LREP    REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
CLMN    Number of Claims: 91
ECL     Exemplary Claim: 1
DRWN    14 Drawing Page(s)
LN.CNT 3652
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI      US 2001051166      A1   20011213                                  <--
        US 6586000         B2   20030701
DETD    . . . substances include the broad classes of compounds normally
        delivered through body surfaces and membranes, including skin. In
        general, this includes: analgesic agents; anesthetic agents;
        antiarthritic agents; respiratory drugs, including antiasthmatic agents;
        anticancer agents, including antineoplastic drugs; anticholinergics;
        anticonvulsants; antidepressants; antidiabetic agents;. . .
DETD    . . . to, amiodarone, amitryptyline, azithromycin, benzphetamine,
        bromopheniramine, chlorambucil, chloroprocaine, chloroquine,
        chlorpheniramine, chlorothen, chlorpromazine, cinnarizine,
        clarthromycin, clomiphene, cyclobenzaprine, cyclopentolate,
        cyclophosphamide, dacarbazine, demeclocycline, dibucaine,
        dicyclomine, diethylproprion, diltiazem, dimenhydrinate,
        diphenhydramine, diphenylpyraline, disopyramide, doxepin, doxycycline,
        doxylamine, dypyridame, ephedrine, epinephrine, ethylene
```

diamine tetraacetic acid (EDTA), erythromycin, flurazepam, gentian violet, hydroxychloroquine, imipramine, isoproterenol, isothipendyl, levomethadyl, **lidocaine**, loxarine, mechlorethamine, melphalan, methadone, methafurylene, methapheniline, methapyrilene, methdilazine, methotimeperazine, methotrexate, metoclopramide, minocycline, naftifine, nicardipine, nicotine, nizatidine, orphenadrine, oxybutynin, oxytetracycline, phenindamine,. . .

DETD . . . homatropine, hydrocodone, hydromorphone, hydroxyzine, hyoscyamine, imipramine, itraconazole, keterolac, ketoconazole, levocarbustine, levorphone, lincomycin, lomefloxacin, loperamide, lorazepam, losartan, loxapine, mazindol, meclizine, meperidine, **mepivacaine**, mesoridazine, methdilazine, methenamine, methimazole, methotrimeperazine, methysergide, metronidazole, midazolam, minoxidil, mitomycin c, molindone, morphine, nafzodone, nalbuphine, naldixic acid, nalmefene, naloxone, naltrexone,. . .

DETD . . . potency corticosteroids such as clobetasol propionate, betamethasone benzoate, betamethasone diproprionate, diflorasone diacetate, fluocinonide, mometasone furoate, triamcinolone acetonide, and the like; **local anesthetic** agents such as phenol, benzocaine, **lidocaine**, **prilocaine** and **dibucaine**; topical **analgesics** such as glycol salicylate, methyl salicylate, 1-menthol, d,1-camphor and capsaicin; and antibiotics. Preferred additional agents are antibiotic agents, discussed in. . .

DETD . . . of the invention to treat any patient with an NSAID-responsive condition or disorder. Typically, NSAIDs are employed as anti-inflammatory and/or **analgesic** agents, and accordingly may be used to treat individuals suffering from rheumatic or arthritic disorders, including, for example: rheumatoid arthritis. . .

DETD . . . inhibition of platelet aggregation). Further non-limiting uses for NSAIDs include either single or adjuvant therapy for ankylosing spondylitis, bursitis, cancer-related **pain**, dysmenorrhea, gout, headaches, muscular **pain**, tendonitis, and **pain** associated with medical procedures such as dental, gynecological, oral, orthopedic, post-partum and urological procedures.

DETD . . . antibiotics (e.g., magainin I and magainin II), anti-fungal agents, anti-psoriatic agents, antipruritic agents, antihistamines, antineoplastic agents (e.g., asparaginase and bleomycin), **local anesthetics**, anti-inflammatory agents and the like.

DETD . . . including, but not limited to, topical antibiotics and other anti-acne agents, anti-fungal agents, anti-psoriatic agents, antipruritic agents, antihistamines, antineoplastic agents, **local anesthetics**, anti-inflammatory agents and the like. Suitable topical antibiotic agents include, but are not limited to, antibiotics of the lincomycin family. . .

DETD [0114] **analgesic** and anesthetic agents--hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, codeine, morphine, alfentanil, fentanyl, meperidine, sufentanil, buprenorphine, and nicomorphine;

DETD . . . nimodipine, bepridil, amlodipine and diltiazem; beta-blockers such as metoprolol; pindolol, propafenone, propranolol, esmolol, sotalol and acebutolol; antiarrhythmics such as moricizine, **ibutilide**, procainamide, quinidine, disopyramide, **lidocaine**, phenytoin, tocainide, mexiletine, flecainide, encainide, bretylium and amiodarone; cardioprotective agents such as dexrazoxane and leucovorin; vasodilators such as nitroglycerin; cholinergic. . .

L17 ANSWER 2 OF 5 USPATFULL

AB In accordance with the present invention, there are provided conjugates of physiologically compatible free radical scavengers (e.g., dithiocarbamate disulfides (DD)) and pharmacologically active agents (e.g., NSAIDS). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective

effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of free radical overproduction induced thereby as a result of the co-production of free radical scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

AN 2001:131342 USPATFULL

TI Conjugates of dithiocarbamate disulfides with pharmacologically active agents and uses therefor

IN Lai, Ching-San, Encinitas, CA, United States
Vassilev, Vassil P., San Diego, CA, United States
Wang, Tingmin, San Marcos, CA, United States

PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)

PI US 6274627 B1 20010814 <--

AI US 1999-416619 19991012 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Reiter, Stephen E.Foley & Lardner

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 2173

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6274627 B1 20010814 <--

SUMM . . . example, although Non-Steroid Anti-Inflammatory Drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, **pain** and fever, NSAIDs (e.g., aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to. . .

SUMM . . . defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to inflammation, **pain** and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the. . .

DETD . . . heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, neurodegenerative disorders (e.g., chronic neurodegenerative disease), chronic **pain**, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, gastrointestinal motility disorders, obesity,. . .

DETD **analgesics**/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride,. . .

DETD . . . encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, **lidocaine** hydrochloride, and the like);

DETD bronchodialators (e.g., sympathomimetics (e.g., **epinephrine** hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate, **epinephrine** bitartrate, metaproterenol sulfate, **epinephrine**, **epinephrine** bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline, dyphylline, metaproterenol sulfate, aminophylline), mast cell stabilizers (e.g., cromolyn sodium), inhalant. . .

DETD . . . isolates (e.g., epocarbazolin-A), superoxide dismutase (e.g.,

EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and **epinephrine** in biodegradable gel-like matrix, and AccuSite), topical formulations (e.g., P-0751, and P-0802), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g.,. . .

DETD . . . stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide, guaifenesin, hydrochlorothiazide, hydrocodone, hydrocortisone, ibuprofen, **ibutilide** fumarate, indapamide, insulin, ipratropium bromide, ketoconazole, ketoprofen, ketorolac tromethamine, lamivudine, lansoprazole, levonorgestrel, levothyroxine, lisinopril, loracarbef, loratidine, lorazepam, losartan potassium, lovastatin,. . .

DETD . . . spondylitis, tendinitis and bursitis, and acute gout. Naproxen sodium, the sodium salt of naproxen, has also been developed as an **analgesic** because it is more rapidly absorbed. The side effects of GI ulceration, bleeding, and perforation is problematic to naproxen and. . .

CLM What is claimed is:

. . . autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, cerebral ischemia, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic **pain**, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, gastrointestinal motility disorders, obesity,. . .

L17 ANSWER 3 OF 5 USPATFULL

AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

AN 2001:90260 USPATFULL

TI Fatty acid-pharmaceutical agent conjugates

IN Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States

PI US 2001002404 A1 20010531 <--
US 6576636 B2 20030610

AI US 2000-730450 A1 20001205 (9)

RLI Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED

DT Utility

FS APPLICATION

LREP Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 14 Drawing Page(s)

LN.CNT 2511

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 2001002404 A1 20010531 <--
US 6576636 B2 20030610

SUMM . . . of pharmaceutical agents include: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; alcohol deterrent; aldosterone antagonist; amino acid; ammonia detoxicant; anabolic; analeptic; **analgesic**; androgen; anesthesia, adjunct to; anesthetic; anorectic; antagonist; anterior pituitary suppressant; anthelmintic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-androgen; anti-anemic; anti-anginal; anti-anxiety;. . . thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; uricosuric; **vasoconstrictor**; vasodilator; vulnerary; wound healing agent;

xanthine oxidase inhibitor.

DETD [0093] Adrenergic: Adrenalone; Amidephrine Mesylate; Apraclonidine Hydrochloride; Brimonidine Tartrate; Dapiprazole Hydrochloride; Deterenol Hydrochloride; Dipivefrin; Dopamine Hydrochloride; Ephedrine Sulfate; **Epinephrine**; **Epinephrine** Bitartrate; Epinephryl Borate; Esproquin Hydrochloride; Etafedrine Hydrochloride; Hydroxyamphetamine Hydrobromide; Levonordefrin; Mephentermine Sulfate; Metaraminol Bitartrate; Metizoline Hydrochloride; Naphazoline Hydrochloride; Norepinephrine Bitartrate;. . .

DETD [0102] **Analgesic**: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine. . .

DETD [0105] Anesthetic: Aliflurane; Benoxinate Hydrochloride; Benzocaine; Biphenamine Hydrochloride; **Bupivacaine** Hydrochloride; Butamben; Butamben Pierate; Chloroprocaine Hydrochloride; Cocaine; Cocaine Hydrochloride; Cyclopropane; Desflurane; Dexivacaine; Diamocaine Cyclamate; **Dibucaine**; **Dibucaine** Hydrochloride; Dyclonine Hydrochloride; Enflurane; Ether; Ethyl Chloride; **Etidocaine**; Etoxadrol Hydrochloride; Euprocin Hydrochloride; Fluroxene; Halothane; Isobutamben; Isoflurane; Ketamine Hydrochloride; Levoxadrol Hydrochloride; **Lidocaine**; **Lidocaine** Hydrochloride; **Mepivacaine** Hydrochloride; Methohexital Sodium; Methoxyflurane; Midazolam Hydrochloride; Midazolam Maleate; Minaxolone; Nitrous Oxide; Norflurane; Octodrine; Oxethazaine; Phencyclidine Hydrochloride; Pramoxine Hydrochloride; **Prilocaine** Hydrochloride; Procaine Hydrochloride; Propanidid; Proparacaine Hydrochloride; Propofol; Propoxycaine Hydrochloride; Pyrrocaine; Risocaine; Rodocaine; Roflurane; Salicyl Alcohol; Sevoflurane; Teflurane; Tetracaine; Tetracaine Hydrochloride;. . .

DETD . . . Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobuline; Edifolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; **Ibutilide** Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium. . .

DETD [0284] **Vasoconstrictor**: Angiotensin Amide; Felypressin; Methysergide; Methysergide Maleate.

DETD . . . lemefloxacin; lemildipine; leminoprazole; lenercept; lenograstim; lentinan sulfate; leptin; leptolstatin; lercanidipine; lerisetron; lesopitron; letrazuril; letrozole; leucomyzin; leuprorelin; levcromakalim; levetiracetam; levobetaxolol; levobunolol; **levobupivacaine**; levocabastine; levocarnitine; levodropropizine; levofloxacin; levomoprolol; levonorgestrel; levormeloxifene; levosimendan; levosulpiride; linotroban; linsidomine; lintitript; lintopride; liothyronine sodium; lirexapride; lisinopril; lobaplatin; lobucavir; lodoxamide;. . . rimantadine; rimexolone; rimoprogin; riodipine; ripisartan; risedronic acid; rispenzepine; risperidone; ritanserin; ritipenem; ritipenem acoxil; ritolukast; ritonavir; rizatriptan benzoate; rohitukine; rokitamycin; ropinirole; **ropivacaine**; roquinimex; roxatidine; roxindole; roxithromycin; rubiginone B1; ruboxyl; rufloxacin; rupatidine; ruzadolane; safingol; safironil; saintopin; salbutamol, R-; salmeterol; salmeterol, R-salnacedin; sameridine; sampatrilat;. . .

DETD . . . symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; amyotrophic lateral sclerosis agents; Paget's disease agents; unstable angina agents; uricosuric; **vasoconstrictor**; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

L17 ANSWER 4 OF 5 USPATFULL

AB In accordance with the present invention, there are provided conjugates

of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of nitric oxide overproduction induced thereby as a result of the co-production of nitric oxide scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

AN 1999:72602 USPATFULL
TI Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5916910 19990629 <--
AI US 1997-869158 19970604 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Davis, Zinna Northington
LREP Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5916910 19990629 <--

SUMM . . . example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, **pain** and fever, NSAIDs (e.g., aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to. . .

SUMM . . . defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to inflammation, **pain** and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the. . .

SUMM . . . disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDA, AIDS dementia, chronic neurodegenerative disease, chronic **pain**, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility. . .

SUMM **analgesics**/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride,. . .

SUMM . . . encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, **lidocaine** hydrochloride, and the like);

SUMM bronchodialators (e.g., sympathomimetics (e.g., **epinephrine** hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate, **epinephrine** bitartrate, metaproterenol sulfate, **epinephrine**, **epinephrine** bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline,

dyphylline, metaproterenol sulfate, aminophylline), mast cell stabilizers (e.g., cromolyn sodium), inhalant. . .

SUMM . . . isolates (e.g., epocarbazolin-A), superoxide dismutase (e.g., EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and **epinephrine** in biodegradable gel-like matrix, and AccuSite), topical formulations (e.g., P-0751, and P-0802), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g.,. . .

SUMM . . . stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide, guaifenesin, hydrochlorothiazide, hydrocodone, hydrocortisone, ibuprofen, **ibutilide** fumarate, indapamide, insulin, ipratropium bromide, ketoconazole, ketoprofen, ketorolac tromethamine, lamivudine, lansoprazole, levonorgestrel, levothyroxine, lisinopril, loracarbef, loratidine, lorazepam, losartan potassium, lovastatin,. . .

CLM What is claimed is:

16. A compound according to claim 1 wherein said pharmacologically active agent is selected from NSAIDs, **analgesics**/antipyretics, sedatives/hypnotics, antianginal agents, antianxiety agents, antidepressants, antipsychotic agents, antimanic agents, antiarrhythmics, antihypertensive drugs, antihistamine/antipruritic drugs, immunosuppressants, antimetabolite cytotoxics, neuroprotective agents,. . .

L17 ANSWER 5 OF 5 USPATFULL

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

AN 1998:98932 USPATFULL

TI DHA-pharmaceutical agent conjugates of taxanes

IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States

PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

PI US 5795909 19980818 <--

AI US 1996-651312 19960522 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Jarvis, William R. A.

LREP Wolf, Greenfield & Sacks, P.C.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 27 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 2451

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5795909 19980818 <--

SUMM . . . of pharmaceutical agents include: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; alcohol deterrent; aldosterone antagonist; amino acid; ammonia detoxicant; anabolic; analeptic; **analgesic**; androgen; anesthesia, adjunct to; anesthetic; anorectic; antagonist; anterior pituitary suppressant; anthelmintic; antiacne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-androgen; anti-anemic; antianginal; anti-anxiety;. . . thyromimetic; tranquilizer; treatment of amyotrophic lateral sclerosis; treatment of cerebral ischemia; treatment of Paget's disease; treatment of unstable angina; uricosuric; **vasoconstrictor**; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

DETD Adrenergic: Adrenalone; Amidephrine Mesylate; Apraclonidine Hydrochloride; Brimonidine Tartrate; Dapiprazole Hydrochloride; Deterenol Hydrochloride; Dipivefrin; Dopamine Hydrochloride; Ephedrine Sulfate; **Epinephrine**; **Epinephrine** Bitartrate; Epinephryl Borate; Esproquin Hydrochloride; Etafedrine Hydrochloride;

Hydroxyamphetamine Hydrobromide; Levonordefrin; Mephentermine Sulfate; Metaraminol Bitartrate; Metizoline Hydrochloride; Naphazoline Hydrochloride; Norepinephrine Bitartrate;. . .

DETD **Analgesic**: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine. . .

DETD Anesthetic: Aliflurane; Benoxinate Hydrochloride; Benzocaine; Biphenamine Hydrochloride; **Bupivacaine** Hydrochloride; Butamben; Butamben Picrate; Chloroprocaine Hydrochloride; Cocaine; Cocaine Hydrochloride; Cyclopropane; Desflurane; Dexivacaine; Diamocaine Cyclamate; **Dibucaine**; **Dibucaine** Hydrochloride; Dyclonine Hydrochloride; Enflurane; Ether; Ethyl Chloride; **Etidocaine**; Etoxadrol Hydrochloride; Euprocin Hydrochloride; Fluroxene; Halothane; Isobutamben; Isoflurane; Ketamine Hydrochloride; Levoxadrol Hydrochloride; **Lidocaine**; **Lidocaine** Hydrochloride; **Mepivacaine** Hydrochloride; Methohexital Sodium; Methoxyflurane; Midazolam Hydrochloride; Midazolam Maleate; Minaxolone; Nitrous Oxide; Norflurane; Octodrine; Oxethazaine; Phencyclidine Hydrochloride; Pramoxine Hydrochloride; **Prilocaine** Hydrochloride; Procaine Hydrochloride; Propanidid; Proparacaine Hydrochloride; Propofol; Propoxycaine Hydrochloride; Pyrrocaine; Risocaine; Rodocaine; Roflurane; Salicyl Alcohol; Sevoflurane; Teflurane; Tetracaine; Tetracaine Hydrochloride;. . .

DETD . . . Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobuline; Edifolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; **Ibutilide** Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium. . .

DETD **Vasoconstrictor**: Angiotensin Amide; Felypressin; Methysergide; Methysergide Maleate.

DETD . . . lemefloxacin; lemildipine; leminoprazole; lenercept; lenograstim; lentinan sulfate; leptin; leptolstatin; lercanidipine; lerisetron; lesopitron; letrazuril; letrozole; leucomyzin; leuprorelin; levcromakalim; levetiracetam; levobetaxolol; levobunolol; **levobupivacaine**; levocabastine; levocamitine; levodropropizine; levofloxacin; levomoprolol; levonorgestrel; levormeloxifene; levosimendan; levosulpiride; linotroban; linsidomine; lintitript; lintopride; liothyronine sodium; lirexapride; lisinopril; lobaplatin; lobucavir; lodoxamide;. . . rimantadine; rimexolone; rimoprogin; riodipine; ripisartan; risedronic acid; rispenzepine; risperidone; ritanserin; ritipenem; ritipenem acoxil; ritolukast; ritonavir; rizatriptan benzoate; rohitukine; rokitamycin; ropinirole; **ropivacaine**; roquinimex; roxatidine; roxindole; roxithromycin; rubiginone B1; ruboxyl; rufloxacin; rupatidine; ruzadolane; safingol; safironil; saintopin; salbutamol, R-; salmeterol; salmeterol, R-sainacedin; sameridine; sampatrilat;. . .

DETD . . . symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; amyotrophic lateral sclerosis agents; Paget's disease agents; unstable angina agents; uricosuric; **vasoconstrictor**; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

=>

1: Acta Anaesthesiol Scand. 1993 May;37(4):350-6.

Enhancement by ischemia of the risk of cardiac disorders, especially fibrillation, in regional anesthesia with bupivacaine.

Freysz M, Timour Q, Bertrix L, Loufoua-Moundanga J, Omar S, Fauco G.

Department of Medical Pharmacology, Claude Bernard University, Lyon, France.

The impairment of intraventricular conduction by bupivacaine may result in reentrant arrhythmias including ventricular fibrillation. The concentrations responsible for serious accidents are high (5.0 to 8.0 micrograms/ml), but likely to be lowered by myocardial ischemia which gives rise to similar disorders. Therefore we did an electrophysiological study of bupivacaine's effects in an ischemic area of the myocardium. Monophasic action potential (MAP) of the ventricular myocardium was recorded in 30 anesthetized, open chest pigs. Conduction time and effective refractory period were also measured. Data were obtained during short periods (10-15 s) of pacing at 18(beats/min, but ventricular beats remained governed by the sinus node in the intervals. Ischemia was produced by occluding the left anterior descending coronary artery completely but transiently (up to 8 min), not far from its origin. Comparison was made between the effects of bupivacaine i.v. (n = 10), ischemia (n = 10) and both factors (n = 10). Two min after injection of bupivacaine 2.0 mg/kg (plasma levels 2.0-3.0 micrograms/ml), the duration of MAP was only slightly (7.5-15%) prolonged and its ischemia-induced shortening only slightly attenuated by bupivacaine. At the same time, conduction time was considerably (75-150%) lengthened and its ischemia-induced lengthening enhanced, so that ventricular fibrillation induced by coronary occlusion occurred sooner (about 100 instead of 300 s) in the presence of bupivacaine. Consequently, bupivacaine should be used only wit caution in individuals whose myocardium is ischemic or liable to ischemia episodes.

PMID: 8322562 [PubMed - indexed for MEDLINE]

Jun 12 2003 10:19:

h cb hg e e e fcg c e e e b b e

1: Anesth Analg. 2000 Feb;90(2):328-32.

Patient-controlled epidural analgesia during labor: the effects of the increase in bolus and lockout interval.

Bernard JM, Le Roux D, Vizquel L, Barthe A, Gonnet JM, Aldebert A, Benani RM, Fossat C, Frouin J.

Departement d'Anesthesie-Reanimation and Clinique Gynecologique et Obstetricale, Polyclinique Jean-Villar, Bruges-Bordeaux, France.

Most studies use a bolus size of <6 mL of 0.125% bu- pivacaine for patient-controlled epidural analgesia (PCEA) during labor. In this double-blinded, randomized study, we compared the efficacy of a larger bolus injected via a PCEA pump to a conventional PCEA setting. By using a combination of 0.125% bupivacaine with 1:800,000 epinephrine and 0.625 microg/mL sufentanil, the first PCEA setting was typical (4 mL/8 min), whereas the othe combined a 12-mL bolus dose and a 25-min lockout interval, i.e., similar maximal hourly dose. Rescue analgesia was provided with 6 mL of 0.25% bupivacaine. Patient satisfaction and pain were scored on verbal and visual analog scales. Data were analyzed from 103 parturients in the 12-mL/25-min group and 100 in the 4-mL/8-min group. In the 12-mL/25-min group, the median pain score on a 0- to 10-cm visual analog scale was lower at 6-cm cervical dilation (1 [range = 0-8] vs 3 [0-8]) and at delivery (1 [0-10] vs 2 [0-10]). Satisfaction was also better (70% vs 38% "excellent" opinions, at 6-cm cervical dilation). Use of the pump (ratio of successful and total demands) was high and similar in both groups. Rescue analgesia was comparable. Doses of analgesics were greater in the 12-mL/25-min group (hourly bupivacaine dose = 13.9 +/- 5.3 [mean+/- SD] vs 9.4 +/- 4.1 mg). No differences were noted between groups for the severity of hypotension, ephedrine requirement, outcome of the delivery, and Apgar scores. IMPLICATIONS: A patient-controlled epidural analgesia setting that allows a parturient to receive an increased analgesic dose improves satisfaction with patient-controlled epidural analgesia during labor.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 10648316 [PubMed - indexed for MEDLINE]

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1: Anesth Analg. 1995 Apr;80(4):657-63.

Bupivacaine hastens the ischemia-induced decrease of the electrical ventricular fibrillation threshold.

Freysz M, Timour Q, Bertrix L, Loufoua J, Aupetit JF, Faucon G.

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Myocardial ischemia sensitizes the cardiotoxic effects of bupivacaine, especially the propensity to ventricular fibrillation. To investigate this sensitization and to elucidate its mechanism, the influence of bupivacaine alone, or associated with ischemia, was studied on electrical fibrillation threshold in anesthetized, open chest pigs. Determination of fibrillation threshold was performed with impulses of 100 ms duration at the rate of 180 bpm, in the absence of ischemia and at the end of increasing periods of ischemia (30, 60, 120, 180 s) obtained by complete occlusion of the left anterior descending coronary artery close to its origin. The effect of bupivacaine (1.00 mg/kg initial dose plus 0.04 mg.kg-1.min-1 over 25 min) was compared to the control in the same animals. This effect corresponded tc 1.4-1.8 micrograms/mL plasma concentrations likely to be observed in humans after regional anesthesia. Bupivacaine significantly increased the fibrillation threshold before coronary occlusion from approximately 7.0 to 9. mA. In contrast, during ischemia the fibrillation threshold was shifted to the left and down, with a hastening of spontaneous fibrillation. Recording of monophasic action potentials in the ischemic area revealed that conduction time was prolonged by more than 100% under the combined influence of ischemia and bupivacaine, whereas the major enhancement of excitability du to ischemia was not attenuated by bupivacine. Therefore, bupivacaine should be used with caution in the condition of ischemia, especially if heart rate is rapid. In the present experiments, tachycardia is another factor in the enhancement of bupivacaine effects on conduction.

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1: Br J Plast Surg. 1999 Jun;52(4):290-3. Related Articles, Link

The efficacy of bupivacaine with adrenaline in reducing pain and bleeding associated with breast reduction: a prospective trial.

Metaxotos NG, Asplund O, Hayes M.

Plastic and Reconstructive Surgery Unit, Charing Cross Hospital, London, UK.

In a randomised, double-blind, placebo-controlled trial, the effect of preoperative local anaesthesia vasoconstrictor infiltration on peri- and postoperative bleeding and postoperative pain was evaluated in 24 consecutive patients undergoing breast reduction. After the induction of general anaesthesia, one breast was infiltrated with a solution of bupivacaine with adrenaline and the other with the same amount of normal saline solution simultaneously. The perioperative blood loss was calculated by weighing swabs, and postoperative drainage was measured at 3, 24 and 48 h by using suction drains. Postoperative pain was assessed using visual analogue scales and verbal response scores at 3, 6, 10 and 24 h post-infiltration. There was a reduction in perioperative blood loss in the breast infiltrated with bupivacaine and adrenaline ($P < 0.01$). The mean blood loss in the drains from the infiltrated breasts was also less than that from the control sides at 3 and 24 h post-infiltration ($P < 0.05$). Pain was significantly less ($P < 0.01$) at 3 h on the local anaesthetic side. At 6, 10 and 24 h, pain tended to be less on the local anaesthetic side, but this did not reach statistical significance. No major complications were seen. Our results confirm a beneficial effect of bupivacaine with adrenaline on peri- and postoperative bleeding as well as in the early postoperative phase of pain.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 10624296 [PubMed - indexed for MEDLINE]

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Extradural blockade with bupivacaine

A double blind trial of bupivacaine with adrenaline 1/200,000, and bupivacaine plain

H. R. Waters N. Rosen D. H. Perkins

Since the introduction of the long acting local analgesic agent LAC43 (bupivacaine) in Scandinavia[1-4]. it has become widely used in this country where it is marketed under the trade name Marcain.

Originally the drug was available only in a concentration of 0.5% with adrenaline 1/200,000, but it is now available in a concentration of 0.25% with adrenaline 1/400,000.

It is now well established that bupivacaine with adrenaline has a considerably longer duration of action than comparable concentrations of other local analgesic agents[5-7]. Although the question of greater toxicity when used without adrenaline was raised, the decision to market bupivacaine only with adrenaline did not seem to be based on previously published work in man and animals[1]. Nor were there any satisfactory series on the duration of action of bupivacaine without adrenaline. In obstetrics, a plain solution might be thought preferable in view of a possible depressant action of adrenaline on uterine activity. Henn & Brattsand[1] showed that local analgesic agents containing adrenaline 1/200,000 were more toxic than plain solutions when injected intravenously, a situation which could occur during paracervical or extradural analgesia.

For these reasons we set out to compare the speed of onset, duration of action and toxicity of 0.5% bupivacaine with adrenaline 1/200,000, with bupivacaine 0.5% without adrenaline when used to produce extradural analgesia for elective surgical procedures.

MATERIALS

Ampoules containing 10ml of test solutions were put up in packets of three alike, by Duncan Flockhart & Evans Ltd and each packet was identified by a code number. The distribution of the two test solutions was in a previously determined random manner, whose code was not broken by the investigators until the end of the trial.

H. R. Waters, MB, BS, FFARCS, N. Rosen, BM, BCh, FFARCS and D. H. Perkins, MB, BS, FFARCS, Department of Anaesthesia, St Mary's Hospital, London W9. Dr Waters' present address is Department of Anaesthesia, St Thomas' Hospital, London, SE1. Dr Rosen's present address is: Department of Anaesthesia, Harvard Medical School, Massachusetts General Hospital, Boston, Mass.

METHODS

The subjects in the trial were patients
ical and general surgical lists, having
in age from 18 to 77 years. All patients
conscious throughout the procedure. P
gesic supplement were withdrawn fro
vasopressor to counteract hypotension

A standardised technique of admini
The patient was prepared in the sitti
with his feet on a stool. Extradural p
2nd or 3rd lumbar interspace, using
extradural space being identified by t
With the bevel of the needle facing i
catheter (36". A.109 Epidural Cannul
the needle until the third mark of the c
needle, which was then withdrawn. A
was injected through the catheter and
the horizontal supine position.

The patient's blood pressure was m
minute interval if signs suggestive of
the remainder of the calculated dose
was calculated from table 1 on the bas
necessary to block. An allowance for
solution to the total dose for patients
tracting 1ml of solution from the total
in height.

TABL

AGE	
20–30 yrs	
30–40 yrs	
40–50 yrs	
50–60 yrs	
over 60 yrs	

Add 1ml for pati
Subtract 1ml for pa
(modified – afte

The time of onset of the first signs o
to pin prick, or subjective change in
time of disappearance of the knee
gives a finite end point in the deve
Where possible, the maximal level the

After surgery the patient remained
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Rosen, BM, BCh, FFARCS and D. H. Perkins, ıaesthesia, St Mary's Hospital, London W9. Dr ' of Anaesthesia, St Thomas' Hospital, London, artment of Anaesthesia, Harvard Medical School, , Mass.

Anaesthesia vol 25 no 2 April 1970

METHODS

The subjects in the trial were patients on routine orthopaedic, gynaecological and general surgical lists, having no intercurrent disease and ranging in age from 18 to 77 years. All patients were un-premedicated and remained conscious throughout the procedure. Patients requiring a sedative or analgesic supplement were withdrawn from the trial. Those who received a vasopressor to counteract hypotension were retained.

A standardised technique of administration of the drug was employed. The patient was prepared in the sitting position on the operating table with his feet on a stool. Extradural puncture was performed through the 2nd or 3rd lumbar interspace, using a Huber-pointed Tuohy needle, the extradural space being identified by the loss of resistance test using air. With the bevel of the needle facing in a cephalad direction a 1mm bore catheter (36". A.109 Epidural Cannula, Portex Ltd) was passed through the needle until the third mark of the catheter was level with the hub of the needle, which was then withdrawn. A test dose of 5ml of the trial solution was injected through the catheter and the patient immediately placed in the horizontal supine position.

The patient's blood pressure was measured frequently and after a five minute interval if signs suggestive of spinal analgesia had not developed, the remainder of the calculated dose of the solution was given. This dose was calculated from table 1 on the basis of the number of segments it was necessary to block. An allowance for height was made by adding 1ml of solution to the total dose for patients taller than 5' 9" (175cm), and subtracting 1ml of solution from the total for patients less than 5' 3" (160cm) in height.

TABLE 1

AGE	DOSE
20–30 yrs	1.2ml per segment
30–40 yrs	1.1ml per segment
40–50 yrs	1.0ml per segment
50–60 yrs	0.9ml per segment
over 60 yrs	0.8ml per segment

Add 1ml for patients over 5' 9"
Subtract 1ml for patients under 5' 3"
(modified – after Bromage[8])

The time of onset of the first signs of analgesia, either by loss of response to pin prick, or subjective change in sensation was recorded, as was the time of disappearance of the knee jerk reflex. The loss of this reflex gives a finite end point in the development of the neuronal blockade. Where possible, the maximal level the block reached was also recorded.

After surgery the patient remained in the recovery unit until the patellar reflex had returned. This time was recorded, as was the time of onset of post-operative pain. Any effects attributable to the extradural anaesthesia were also noted.

RESULTS

Seventy-three patients were included in this study, but when the data were analysed only forty-three were sufficiently complete for inclusion. Of these twenty had received bupivacaine with adrenaline and twenty-three had received bupivacaine alone.

Table 2 shows the time intervals from the administration of the test dose to the first signs of blockade, the loss of the knee jerk reflex and to the time of maximal extension of the block. The first signs appeared significantly sooner with the bupivacaine plain, by a mean of 2.2 minutes. With regard to the loss of knee jerk and the completion of the block, there is no statistical significance in the small differences in latency between bupivacaine with and without adrenaline.

Table 3 shows in minutes, the duration of the block from the time of administration of the test dose.

TABLE 2

Onset (minutes) – FROM THE TIME OF THE TEST DOSE

	TREATMENT	RANGE	MEAN	NO OF CASES	S.E OF MEAN	t*	p
First signs	B+A	3–20	12.2	21	1.08	1.67	<0.1
	B	3–28	10.0	22	1.06		
Loss of knee jerk	B+A	8–26	19.0	21	1.31	1.33	NS
	B	13–35	21.5	22	1.28		
Complete	B+A	14–45	28.3	21	2.03	1.22	NS
	B	15–50	28.1	22	1.98		

A=adrenaline 1:200,000 *two-tailed test
B=bupivacaine 0.5%

TABLE 3

Duration (minutes) – FROM THE TIME OF THE TEST DOSE

	TREATMENT	RANGE	MEAN	NO OF CASES	S.E OF MEAN	t*	p
Return of response to pin-prick	B+A	70–260	127	21	8.43	0.32	NS
	B	69–162	124	22	8.24		
Return of knee jerk	B+A	148–338	235	21	11.9	2.41	<0.02
	B	105–310	194	21	11.9		
Onset of post-op. pain	B+A	145–440	261	17	23.4	1.22	NS
	B	89–575	222	18	22.7		

A=adrenaline 1:200,000 *one-tailed test
B=bupivacaine 0.5%

TYPE OF OPERATION	CASE NUMBER	SEX	AGE	TOTAL DOSE ML	HEIGHT OF BLOCK	VASO-PRESSOR	SIDE EFFECTS
DRUG Bupivacaine Plain							
VARICOSE VEINS	1	F	31	18	T4		Shivering before full dose
	2	F	36	17	T12		Shivering
	3	F	32	16	T8		None
HERNIAS AND HYDROCOELES	4	M	55	19	T7		Shivering
	5	M	40	15	T10		Sweating, shivering
	6	M	29	18	T4		Shivering
	7	M	28	17	T9		Asleep
	8	M	47	16	T6		None
	9	M	25	21	T10		None
	10	M	50	19	T10		Shivering
	11	M	49	19	T10		None
ORTHOPAEDIC	12	M	61	16.5	T5		None
Loose body in the knee	13	F	64	12	T8		None, asleep
Kellers	14	F	65	16	T4		Tinnitus, nausea, slurred speech, BP 60/40
Austin Moore	15	M	32	18	L1	X1	None
Menisectomy	16	M	18	19	T10		None
Ankle arthrodesis	17	M	32	20	T10		Shivering
LOWER ABDOMINAL	18	F	57	17.5	T3		Vomited, faintness, shivering, BP 60/30
Hemicolectomy	19	F	42	18	T3	X3	Shivering, vomited
Hysterectomy	20	F	72	14	T9		Shivering

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TABLE 2

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GE	MEAN	NO OF CASES	S.E OF MEAN	t*	p
20	12.2	21	1.08	1.67	<0.1
28	10.0	22	1.06		
26	19.0	21	1.31	1.33	NS
35	21.5	22	1.28		
45	28.3	21	2.03	1.22	NS
50	28.1	22	1.98		

*two-tailed test

TABLE 3

FROM THE TIME OF THE TEST DOSE

GE	MEAN	NO OF CASES	S.E OF MEAN	t*	p
60	127	21	8.43	0.32	NS
62	124	22	8.24		
38	235	21	11.9	2.41	<0.02
10	194	21	11.9		
40	261	17	23.4	1.22	NS
75	222	18	22.7		

*one-tailed test

TYPE OF OPERATION	CASE NUMBER	SEX	AGE	TOTAL DOSE ML	HEIGHT OF BLOCK	VASO-PRESSOR	SIDE EFFECTS
DRUG Bupivacaine Plain							
VARICOSE VEINS	1	F	31	18	T4		Shivering before full dose
	2	F	36	17	T12		Shivering
	3	F	32	16	T8		None
	4	M	55	19	T7		Shivering
HERNIAS AND HYDROCOELES	5	M	40	15	T10		Sweating, shivering
	6	M	29	18	T4		Shivering
	7	M	28	17	T9		Asleep
	8	M	47	16	T6		None
	9	M	25	21	T10		None
	10	M	50	19	T10		Shivering
	11	M	49	19	T10		None
ORTHOPAEDIC	12	M	61	16.5	T5		None
Loose body in the knee	13	F	64	12	T8		None, asleep
Kellers	14	F	65	16	T4	X1	Tinnitus, nausea, slurred speech, BP 60/40
Austin Moore	15	M	32	18	L1		None
Menisectomy	16	M	18	19	T10		None
Menisectomy	17	M	32	20	T10		Shivering
Ankle arthrodesis	18	F	57	17.5	T3	X3	Vomited, faintness, shivering, BP 60/30
LOWER ABDOMINAL	19	F	42	18	T3		Shivering, vomited
Hemicolectomy	20	M	72	15	T8		Shivering
Hysterectomy	21	M	46	17	T11		None
Prostatectomy	22	F	73	13.5	T9		Asleep
Haemarroidectomy	23	F	51	16	T10		Shivering
Radical vulvectomy							
Vaginal repair							
DRUG Bupivacaine with adrenaline 1:200,000							
HERNIAS AND HYDROCOELES	24	F	25	18	T9		Shivering, previous spinal tap, 24 hrs post-spinal headache
	25	M	47	16	T10		None
	26	M	39	20	T5		None
	27	M	65	15	T10		None
	28	M	50	19	T10		None, asleep
	29	M	65	16	T10		None
	30	M	35	19	T10		Shivering
ORTHOPAEDIC	31	F	71	17	T5	X2	Asleep
Austin Moore	32	F	62	15.5	T4	X2	Vertigo, sweating, shivering, BP 60/40
Austin Moore	33	M	36	19	T6		Shivering
McKee	34	M	35	20	T10		None
Bilateral arthrotomy							
LOWER ABDOMINAL	35	F	31	20	T6		Tremor, asleep
Ureteric exploration	36	M	61	14	T5		Shivering, asleep
Cystoscopy	37	M	58	15	T6		Shivering
Prostatectomy	38	M	55	15	T7		Asleep
Vaginal repair	39	F	66	15	T6		Asleep
Prostatectomy	40	F	31	17	T8		Shivering
Myomectomy	41	F	54	18	T9		Shivering, nausea, vomited
Abdominal hysterectomy	42	F	50	16	T8		Shivering, nausea
Vaginal hysterectomy	43	F		16.5	T10		Shivering
Vaginal hysterectomy							

Table 4 shows the extent of the extradural block, the dose of drug given, the nature of the operation and any side effects. Toxic effects on the central nervous system or cardiovascular system[9] directly attributable to the drug were not found in the doses used. About one third of the patients in each group exhibited shivering during the procedure. Four patients had vertigo and slurred speech associated with systolic blood pressures in the region of 60mm Hg. These reactions were equally divided between the two groups of patients and in each case the extradural block extended to the third or fourth thoracic segments. All these patients responded to the administration of oxygen and vasopressors[10].

DISCUSSION

The use of premedicant drugs, supplementary analgesics and sedatives during surgery was deliberately avoided. In this way, one could be sure that the analgesic effects and any toxic side effects were due solely to the drugs being compared. Approximately 20% of the patients fell asleep during the surgery and would not have benefited from heavy sedation or general anaesthesia.

Although the onset of the first signs of analgesia was statistically significantly slower for bupivacaine with adrenaline 1/200,000, the mean difference of 2.2 minutes is obviously not of any clinical importance. It is however, worthwhile noting that this result is a reversal of the situation that is often forecast on a pharmacological basis.

Using pin-prick as the method of assessment of onset of analgesia, other workers[2,7] have obtained similar results for the latency of bupivacaine with adrenaline. Watt *et al*[5] using bupivacaine with adrenaline, found that the time taken for the abolition of the knee jerk lay between five and fifteen minutes. This is a little shorter than the 19 minutes obtained in this trial. However, if the five minute interval between test dose and final dose is subtracted to give a mean of 14 minutes, the difference for practical purposes, is eliminated.

The duration of action of any local analgesic drug used in extradural blockade must inevitably depend on the end point selected for measurement. We chose the return of the knee jerk reflex as the most reliable end-point as it does not depend on the co-operation of the patient, or on the patient's interpretation of pain. Using this end-point, a mean time of duration of action of 235 minutes was obtained for bupivacaine with adrenaline 1/200,000 and 194 minutes for bupivacaine plain. The difference of 41 minutes is statistically significant but would probably be of clinical importance only where the 'single-shot' technique of extradural analgesia is employed. The mean duration of action of bupivacaine with adrenaline of 235 minutes is comparable to the results of other workers. For example, Rubin & Lawson[6] using pin-prick assessment of the reduction of the extent of sensory block by at least two s
of 229 minutes.

The duration of action as measured
is approximately 40 minutes longer fo
minutes) than for bupivacaine plain (2
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measuring the interval before the first
However, the situation was very differe
in that the durations of action he mea
hours.

SIDE EFFECTS

No serious toxic signs were seen in t
centrations used. However, the 50 per
some comment. Downing[12] noted an i
when using bupivacaine 0.5 per cent c
extradural blockade. His patients did h
and supplementary drugs. In this trial,
groups of patients. Whether one rega
not, it was neither enhanced nor red
However, being unpremedicated, the
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Downing[12].

In the majority of cases the shivering
operation and may have been purely
when the patient was covered with
theatre at 19°C (70°F), the exposure of
and the resultant vasodilatation from
siderable heat loss. Unfortunately we
in this investigation.

In view of these results there would
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who wish to use it for extradural block

SUMMARY

Data are presented from a double bli
lumbar extradural blockade using eithe
1/200,000 or bupivacaine 0.5% plain
elective surgical procedures and receive

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The duration of action as measured by the return of post-operative pain is approximately 40 minutes longer for bupivacaine with adrenaline (261 minutes) than for bupivacaine plain (222 minutes). This end-point is not as reliable and in this trial the difference is not statistically significant due to greater variability. Telivuo[11] using similar solutions for post-thoracotomy intercostal blocks, found that bupivacaine with adrenaline gave a duration of action 100 minutes longer than bupivacaine plain, measuring the interval before the first post-operative analgesic was given. However, the situation was very different from that of extradural blockade in that the durations of action he measured were in the region of 10 to 16 hours.

SIDE EFFECTS

No serious toxic signs were seen in this trial with the dosages and concentrations used. However, the 50 per cent incidence of shivering requires some comment. Downing[12] noted an incidence of shivering of 20 per cent when using bupivacaine 0.5 per cent or 0.25 per cent with adrenaline for extradural blockade. His patients did however, receive both premedication and supplementary drugs. In this trial, the incidence was the same in both groups of patients. Whether one regards this as a toxic manifestation or not, it was neither enhanced nor reduced by the addition of adrenaline. However, being unpremedicated, the patients may have had generally higher levels of endogenous catecholamines than those reported by Downing[12].

In the majority of cases the shivering occurred early in the course of the operation and may have been purely due to body cooling which ceased when the patient was covered with operating towels. In an operating theatre at 19°C (70°F), the exposure of the patient for extradural puncture and the resultant vasodilatation from the blockade could result in considerable heat loss. Unfortunately we did not measure body temperature in this investigation.

In view of these results there would seem to be no reason why bupivacaine without adrenaline should not be made available to those operators who wish to use it for extradural blockade.

SUMMARY

Data are presented from a double blind trial of 43 patients who received lumbar extradural blockade using either bupivacaine 0.5% with adrenaline 1/200,000 or bupivacaine 0.5% plain. The patients were undergoing elective surgical procedures and received no other drugs.

The speed of onset, the duration of analgesia and the incidence of side effects were studied. Using the return of the knee jerk as end-point, the duration of analgesia was significantly longer when adrenaline was added, than when bupivacaine was used alone. No toxic effects attributable to the drugs were observed.

Acknowledgements

The authors are indebted to the surgeons and staff of St Mary's Hospital for their help and co-operation, Mr Graham Williams and associates of Duncan Flockhart & Evans Ltd, for generous supplies of bupivacaine and statistical analysis; and Valerie Page for her work on the manuscript.

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Carb n dioxide salts of li plexus block

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Among the criticisms which are leve time spent waiting for the onset of certain rate of failure are frequently

One of the authors had occasion action of carbonated local analge caine) in extradural blockade as do ported his findings[1,2]. Compared salts of local analgesics the carbon agent by one third and produced a m ade. There was a tendency to wider s total dose. The results were so impr these same solutions in peripheral n chose regional analgesia of the brach

Theory of carbonated local analges

It has been known for a long time t an important factor in the uptake 1892[3] mentioned cocaine with alkali how alkalinised solutions worked. T esics has been ably put forward by this case lignocaine carbonate, have thus less demanding on the buffering the commonly available local ana taining vasoconstrictor agents have no vasoconstrictor are not higher th the free base is liberated quickly due carbon dioxide diffuses very rapidly in the vicinity. Thus the analgesic membrane in a higher concentration In addition carbon dioxide appears by stabilizing excitable tissue.

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